UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,084	12/05/2005	Christine Vauthier	BJS-5006-5	9469

23117 7590 04/08/2009
NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
04/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,084	VAUTHIER ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 5-23* is/are pending in the application.

4a) Of the above claim(s) *7,11-14,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,8-10,15,16 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *December 23, 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restrictions

Applicant had elected with traverse the invention of Group I, Claims 1-10, drawn to a compound comprising a hemoprotein associated with a sequenced block copolymer comprising a hydrophilic segment that is an oligosaccharide or a polysaccharide linked to at least one hydrophobic segment of Formula I and a method of using said compound as a human or animal blood substitute.

Within Group I, Applicant has elected:

i) the "X" moiety species to be CN, as recited in Claims 1 and 4;

ii) the "Y" moiety species to be of the formula "COOR-prime", as recited in Claim 1.

iii) the hemoprotein species "i", wherein the hemoprotein is a "normal hemoprotein" as recited in Claim 2, and

iv) the hydrophilic segment species "ix", wherein the hydrophilic segment is heparin, as recited in Claim 6.

Amendments

In the reply filed December 23, 2008, Applicant has cancelled Claims 3-4, withdrawn Claims 7, 11-14 and17-18, amended Claim 1, and added new claims, Claims 20-23.

Claims 7, 11-14 and 17-18 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-2, 5-6, 8-10, 15-16 and 19-23 are under consideration.

Priority

Acknowledgement is made of the certified translation, filed on April 17, 2007, of the French patent FR 02/11518 filed on September 17, 2002.

Accordingly, the effective priority date of the instant application is granted as September 17, 2002.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on December 23, 2008 that has been considered. The signed and initialed PTO Form 1449 is mailed with this action.

Specification

1. **The amendment filed December 23, 2008 is objected to under 35 U.S.C. 132(a)** because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the amendment attempts to introduce subject matter from foreign application WO 02/39979 regarding the oligo- and/or poly-saccharide. However, support for this amendment cannot be found in the originally filed application, PCT/FR03/01435, or the originally filed specification of the instant application.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

2. **The attempt to incorporate subject matter into this application by reference to WO 02/39979 is ineffective** because the originally filed specification fails to express a clear intent to incorporate by reference the subject matter of WO 02/39979 by using the root words "incorporat(e)" and "reference", e.g. "incorporate by reference". A mere reference to material does not convey an intent to incorporate the material by reference. (1.57(g)(1)). It is noted that the portion(s) of WO 02/33979 that Applicant attempts to introduce into the instant specification and claims discloses a broad genus of oligo- and poly-saccharides. Furthermore, neither the originally filed specification or claims of the originally filed application, PCT/FR03/01435, nor the instant application provide support for the broadly disclosed genus in WO 02/33979, nor the picking and choosing of newly added claim limitations "poly(N-acetylneuraminic acid), amylase, chitosan, pectin or hyaluronic acid" species from said broadly disclosed genus.

The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

Claim Rejections - 35 USC § 112

3. **The prior rejection of Claim 3 under 35 U.S.C. 112, second paragraph is withdrawn** in light of Applicant's amendment to cancel the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New matter

4. **Claims 21-23 are rejected under 35 U.S.C. 112 first paragraph**, because the specification as originally filed does not describe the invention as now claimed.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "WHENEVER THE ISSUE ARISES, THE FUNDAMENTAL FACTUAL INQUIRY IS WHETHER A CLAIM DEFINES AN INVENTION THAT IS CLEARLY CONVEYED TO THOSE SKILLED IN THE ART AT THE TIME THE APPLICATION WAS FILED...IF A CLAIM IS AMENDED TO INCLUDE SUBJECT MATTER, LIMITATIONS, OR TERMINOLOGY NOT PRESENT IN THE APPLICATION AS FILED, INVOLVING A DEPARTURE FROM, ADDITION TO, OR DELETION FROM THE DISCLOSURE OF THE APPLICATION AS FILED, THE EXAMINER SHOULD CONCLUDE THAT THE CLAIMED SUBJECT MATTER IS NOT DESCRIBED IN THAT APPLICATION". MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure*" (emphasis added).

In the instant case, Claims 21-23, added by amendment on December 23, 2008, recite a nanoparticle product comprising an oligo- or poly-saccharide, wherein the oligo- or poly-saccharide may be dextran, heparin, poly(N-acetylneuraminic acid), amylose, chitosan, pectin or hyaluronic acid. Neither the originally filed specification or claims of the originally filed application, PCT/FR03/01435, nor the instant application provide clear and unambiguous support for the broadly disclosed genus in WO 02/33979, nor the picking and choosing of newly

added claim limitations "poly(N-acetylneuraminic acid), amylase, chitosan, pectin or hyaluronic acid" species from said broadly disclosed genus (see discussions above). Accordingly, Claims 21-23 are considered to constitute new matter. Thus, the amendment is a departure from or an addition to the disclosure of the application as filed, accordingly, it introduces new matter into the disclosure.

For reasons set forth above, the amendment filed December 23, 2008 is objected to under 35 U.S.C. §132 because it introduces new matter into the disclosure. 35 U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the invention. Applicant is required to cancel the new matter in the reply to this Office Action.

Alternatively, if Applicant believes that support for a nanoparticle product comprising an oligo- or poly-saccharide, wherein the oligo- or poly-saccharide may be poly(N-acetylneuraminic acid), amylose, chitosan, pectin or hyaluronic acid is present and clearly envisaged in the instant application or earlier filed priority documents, applicant must, in responding to this Office Action, point out with particularity, where such support may be found.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. **The prior rejection of Claims 1-2, 5-6, 8-10, 15-16 and 19 under 35 U.S.C. 103(a)** as being obvious over Chauvierre et al (WO 02/39979 A1; *of record, U.S. equivalent is 2004/0028635) and Desai et al (U. S. Patent No. 6,096,331; *of record) **is withdrawn** in light of Applicant's arguments that the means by which the hemoprotein is associated with the heparin in

the particle of Desai et al is by covalent linkage as a result of the ultrasonic irradiation process, which, upon further review and consideration of the Desai et al reference, the Examiner finds persuasive. Thus, Desai et al teach away from a non-covalent association between heparin polysaccharide and hemoglobin.

6. **Claims 1-2, 5-6, 8-10, 15-16 and 19-23 are rejected under 35 U.S.C. 103(a)** as being obvious over Chauvierre et al (WO 02/39979 A1; *of record, U.S. equivalent is 2004/0028635) and Schmidt et al (U.S. Patent 4,698,387) and Desai et al (U. S. Patent No. 6,096,331; *of record).

This is a new rejection.

Determining the scope and contents of the prior art.

Chauvierre et al teach the synthesis of nanoparticles of 1nm to 1mm [0045-46] comprising a core portion and a surface portion forming a sequenced block copolymer, said core portion comprising at least one hydrophobic segment having the formula as taught in Formula I, wherein "X" may be a "CN" moiety, wherein the hydrophobic segment may be a poly(alkylcyanoacrylate) [0010-0019], [0039] [0043-44] conjugated to a saccharide hydrophilic that may be heparin [0028]. Chauvierre et al teach that the inventive delivery system(s) may be used to administer a therapeutic agent to an animal or patient [0049-50].

Chauvierre et al do not teach the use of the heparin-coated poly(cyanoacrylate) nanoparticle for the delivery of hemoproteins such as hemoglobin, wherein the hemoglobin is non-covalently associated with the polysaccharide. However, at the time of the invention, Schmidt et al disclosed a composition comprising a conjugate between hemoglobin and an adduct comprising an anionic ligand and a macromolecular agent, wherein the macromolecular agent may be a polysaccharide (col. 4, lines 6-13). The macromolecular agent is chemically linked with an adduct ligand, thereby binding hemoglobin by way of a non-covalent bond (col. 4, lines 39-45). The hemoglobin conjugates can be used as hemoglobin-containing blood substitutes, and are able to reversibly bind and release molecular oxygen (col. 5, lines 25-27). The intended use of the product is a blood substitute suitable as an oxygen and carbon dioxide carrier (col. 3, lines 18-20), and thus said product is "gas-associated".

Neither Chauvierre et al nor Schmidt et al disclose the blood substitute product to comprise saline. However, at the time of the invention, Desai et al taught the synthesis of

nanoparticles comprising synthetic block copolymers (col. 10, lines 3-22), attached to biocompatible materials, i.e. polysaccharides (col. 9, lines 42-49) to form a polymeric shell. Desai et al also contemplate that hemoglobin would be associated with the polymeric shell (col. 9, line 54; col. 11, line 63), thereby providing a blood substitute. Given that Desai et al contemplate the use of a hemoglobin-containing nanoparticle for use as a blood substitute, one of ordinary skill in the art would reasonably expect said composition to be "gas-associated". Desai et al disclose the nanoparticle product may diluted in saline for delivery (col. 6, line 29; col. 11, lines 10-13; Example 6, col. 17, line 15; Example 12, col. 21, lines 3-4).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in synthesizing nanoparticles and artificial blood substitutes for therapeutic purposes. Therefore, the level of ordinary skill in this art is high.

The instant claims are drawn to particle product comprising a co-polymer non-covalently associated with a hemoprotein. However, the term "comprising" is open-ended and allows for additional, unrecited elements in the claims. MPEP 2111.03 specifically sets forth that the transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004). Schmidt et al disclose the use of a ligand covalently attached to the polysaccharide, whereupon the hemoprotein is non-covalently associated with the ligand, thereby achieving hemoprotein non-covalently associated with the surface portion of a particle. The instant specification and claims fail to specifically exclude the structural limitations of a hemoprotein ligand (Schmidt et al) through which the hemoprotein may form a non-covalent association with the polysaccharide-coated co-polymer (Chauvierre et al).

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to modify the heparin-coated poly(cyanoacrylate) nanoparticle of Chauvierre et al to comprise hemoglobin conjugated

non-covalently as taught by Schmidt et al for the formation of a blood substitute product with a reasonable chance of success because Schmidt et al successfully demonstrate that the manufacture of polysaccharide-ligand-hemoglobin conjugates for the formation of a blood substitute in which the hemoglobin is attached non-covalently to the polysaccharide. Applicant's own work teaches that prior to the instantly asserted invention, the art had long recognized that heparin, being polyanionic in nature, has a high affinity for basic proteins like hemoglobin (Haney et al, 2000; reference 19 of Chauvierre et al, 2004a; * of record), and thus those of ordinary skill in the art would immediately recognize a reasonable expectation of success for the formation of a non-covalent association between hemoglobin and heparin. An artisan would have been motivated to modify the heparin-coated poly(cyanoacrylate) nanoparticle of Chauvierre et al to comprise hemoglobin conjugated non-covalently as per Schmidt et al for the formation of a blood substitute product because the heparin moiety, well known in the art to act as an anti-coagulant as well as to inhibit complement activation, already tailors the nanoparticle for increased circulating half-life of the nanoparticle, and thus would provide an artisan with the desired delivery vehicle for a blood substitute, and Schmidt et al disclose that all of the hemoglobin-containing molecules comprising a covalent bond between the cross-linking agent or polymer results in a change in the hemoglobin structure, thereby adversely affecting oxygen transport, impairing oxygen release, reduced hemoglobin cooperativity, and an undesired increase in oxygen affinity disadvantageous for use as a blood substitute (col. 2, lines 16-53). The non-covalent association of hemoglobin with the polysaccharide-ligand overcomes the art-recognized disadvantageous properties.

It also would have been obvious to one of ordinary skill in the art to substitute a carrier/buffer as taught by Chauvierre et al and/or Schmidt et al with saline as taught by Desai et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re*

Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, those of ordinary skill in the art have long-recognized saline to be a pharmaceutically acceptable carrier/buffer for the delivery of pharmaceutical compositions, and saline (Desai et al) would perform the same art-recognized functions as the carriers/buffers of Chauvierre et al and/or Schmidt et al.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Examiner, Art Unit 1633